

## REMARKS

Applicants respectfully request entry of the amendments and remarks presented herein. The specification is amended to replace the term "kD" with "kDa" throughout. The heading for Example 12 at page 26 of the specification also is amended to correct a typographical error.

Claims 37-55 and 74-79 stand rejected. Claims 38-42 and 74-79 are cancelled herein without prejudice. Claim 37 is amended to incorporate language from previous claim 43, and recites that the binding interaction between the hydroxyalkylstarch (HAS) molecule and the protein is a covalent bonding which is the result of a coupling reaction between (i) the terminal aldehyde group of the HAS molecule and (ii) a primary amino group of the protein to form a Schiff's base. Claim 43 has been amended for consistency with claim 37. Claims 44-47 are amended to replace the term "kD" with "kDa." No new matter has been added.

In light of these amendments and the following remarks, Applicants respectfully request reconsideration and allowance of claims 37 and 43-55.

### Objections to the Specification

The Examiner objected to the specification, stating that molecular mass should be abbreviated as "kDa" rather than "kD." The Examiner also objected to the Abstract, stating that the last sentence of the Abstract includes legal phraseology.

Applicants have amended the specification to replace the term "kD" with "kDa." Applicants also have removed the term "said" from the last sentence of the Abstract. In light of these amendments, Applicants respectfully request withdrawal of the objections to the specification.

### Claim Objections

The Examiner objected to claims 44-47, asserting that molecular mass should be abbreviated as "kDa" rather than "kD."

Applicants have amended claims 44-47 to replace the term "kD" with "kDa." In light of these amendments, Applicants request withdrawal of the objection to the claims.

### Double Patenting

The Examiner rejected claims 37, 41, 42, 44, 45, 48-53, 55, 74, 78, and 79 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1 and 6-11 of U.S. Patent No 6,083,909 (the '909 patent).

To further prosecution, the present claims have been amended to recite that the HAS and the protein are covalently bonded by a coupling reaction between the terminal aldehyde group of the HAS molecule and a primary amino group of the protein to form a Schiff's base. In contrast, the claims of the '909 patent recite that the protein (hemoglobin) and the hydroxyethylstarch (HES) are linked via amide bonds. The claims of the '909 patent do not recite linking HAS to a protein via a Schiff's base. Thus, the presently claimed conjugates are not obvious variants of the conjugates recited in claims 1 and 6-11 of the '909 patent.

In light of the above, Applicants respectfully request withdrawal of this rejection of claims 37, 44, 45, 48-53, and 55 for obviousness-type double patenting.

The Examiner provisionally rejected claims 37, 39, 41-55, 74-76, 78, and 79 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 86 and 87 of copending Application No 10/472,002 (the '002 application).

Again, the present claims recite that the HAS and the protein are covalently bonded by a coupling reaction between the terminal aldehyde group of the HAS molecule and a primary amino group of the protein to form a Schiff's base. Claims 86 and 87 of the '002 application depend from claims 73-85, which recite providing an oxidized HAS that includes at least one reducing end group, and reacting the oxidized HAS with an active ingredient. Since the oxidized HAS is reacted, no Schiff's base can be obtained. Thus, the presently claimed conjugates are not obvious variants of the conjugates recited in claims 86 and 87 of the '002 application.

In light of the above, Applicants respectfully request withdrawal of this rejection of claims 37 and 43-55 for obviousness-type double patenting.

The Examiner provisionally rejected claims 37-39, 41-53, 55, 74-76, 78, and 79 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 37-50, 54, 56, and 74-78 of copending Application No 10/506,366 (the '366 application).

Applicants respectfully request that this rejection be held in abeyance until the claims are otherwise allowable.

The Examiner provisionally rejected claims 37-39, 41-43, 50-55, 74-76, and 79 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 5-8, 21, and 22 of copending Application No 10/567,265 (the '265 application).

Again, the present claims recite that the HAS and the protein are covalently bonded by a coupling reaction between the terminal aldehyde group of the HAS molecule and a primary amino group of the protein to form a Schiff's base. Thus, the HAS and the protein are directly linked. The claims of the '265 application recite conjugates including a "polymer," which can be a polysaccharide, and a protein, wherein a linker is present between the polymer and the protein. The claims of the '265 application fail to recite any conjugate in which a protein is directly linked to a HAS molecule, let alone via a Schiff's base. Thus, the presently claimed conjugates are not obvious variants of the conjugates recited in claims 5-8, 21, and 22 of the '265 application.

In light of the above, Applicants respectfully request withdrawal of this rejection of claims 37, 43, and 50-55 for obviousness-type double patenting.

The Examiner provisionally rejected claims 37-55 and 74-79 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1, 2, 5, 8, 12, 15-18, 44, 45, 47-53, 55, 56, 58-61, and 81-85 of copending Application No 11/078,582 (the '582 application).

The claims of the '582 application recite that HAS is conjugated to erythropoietin (EPO) via a thioether or a carbohydrate moiety. The present claims do not recite conjugation via a thioether or a carbohydrate moiety. Thus, the presently recited conjugates are not obvious

variants of the conjugates recited in claims 1, 2, 5, 8, 12, 15-18, 44, 45, 47-53, 55, 56, 58-61, and 81-85 of the '582 application.

In light of the above, Applicants respectfully request withdrawal of this rejection of claims 37 and 43-55 for obviousness-type double patenting.

The Examiner rejected claims 37-39, 41-55, 74-76, 78, and 79 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 34-50 of copending Application No. 11/078,098 (the '098 application).

As discussed above, the present claims recite that the HAS and the protein are covalently bonded by a coupling reaction between the terminal aldehyde group of the HAS molecule and a primary amino group of the protein to form a Schiff's base. The HAS derivatives recited in the claims of the '098 application comprise a linker between the HAS and the protein. The claims of the '098 application do not recite any conjugate in which a protein is directly linked to a HAS molecule, let alone linked via a Schiff's base. Thus, the presently claimed conjugates are not obvious variants of the HAS derivatives recited in claims 34-50 of the '098 application.

In light of the above, Applicants respectfully request withdrawal of this rejection of claims 37 and 43-55 for obviousness-type double patenting.

The Examiner provisionally rejected claims 37-55 and 74-79 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 25-36 and 38-59 of copending Application No. 11/518,352 (the '352 application).

The present claims recite conjugates in which the HAS and the protein are covalently bonded by a coupling reaction between the terminal aldehyde group of the HAS molecule and a primary amino group of the protein to form a Schiff's base. In contrast, the polymer-protein conjugates recited in claims 25-36 and 38-55 and 57-59 of the '352 application include a linker between the polymer and the protein. Thus, the presently claimed conjugates are not obvious variants of the conjugates recited in claims 25-36, 38-55, and 57-59 of the '352 application.

Although the conjugate recited in claim 56 of the '352 application does include an amine bond between the HAS and the protein, claim 56 recites that the carbon atom linked to the amine

group is derived from an aldehyde group that was introduced in the polymer by a ring-opening oxidation reaction. As such, it is not the terminal aldehyde group of the HAS that is reacted with the amine group of the protein. As such, the presently claimed conjugates are not obvious variants of the conjugate recited in claim 56 of the '352 application.

In light of the above, Applicants respectfully request withdrawal of this rejection of claims 37 and 43-55 for obviousness-type double patenting.

The Examiner provisionally rejected claims 37-55 and 74-79 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 13-22 and 24-31 of copending Application No. 11/530,264 (the '264 application).

Again, the present claims recite that the HAS and the protein are covalently bonded by a coupling reaction between the terminal aldehyde group of the HAS molecule and a primary amino group of the protein to form a Schiff's base. The claims of the '264 application recite HAS-active substance conjugates that are prepared by reacting a thioester group with an alpha-X beta amino group. The claims of the '264 application do not recite a conjugate in which a protein and a HAS molecule are linked via a Schiff's base formed between the terminal aldehyde of the HAS and a primary amino group of the protein. Thus, the presently claimed conjugates are not obvious variants of the conjugates recited in claims 13-22 and 24-31 of the '264 application.

In light of the above, Applicants respectfully request withdrawal of this rejection of claims 37 and 43-55 for obviousness-type double patenting.

#### Rejections under 35 U.S.C. § 112

The Examiner rejected claims 37-55 and 74-79 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. In particular, the Examiner asserted that in claims 37 and 74, it is unclear how the conjugate is "based on" a covalent bond, and that at the end of claim 37, it is unclear what "appropriate" might be. The Examiner also asserted that in claims 40 and 77, it is unclear if the functional group is introduced by recombinant techniques or if the amino acid

sequence is recombinantly modified and then the functional group reacts with the modified amino acid sequence, and that it is unclear what "original" is. In addition, the Examiner asserted that in claims 48 and 49, it is unclear what the HAS is being substituted with.

Applicants have amended claim 37 to remove the terms "based on" and "appropriate." Claim 40 is cancelled. As such, this rejection of claims 37 and 40 is moot.

Applicants disagree with the rejection of claims 48 and 49. The specification at page 6, lines 16-18 clearly discloses that the degree of substitution is the ratio of the number of modified anhydroglucose units to the number of anhydroglucose units in total. Thus, the meaning of "degree of substitution" is clear, and claims 48 and 49 are sufficiently definite.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 37 and 43-55 under 35 U.S.C. § 112, second paragraph.

The Examiner rejected claims 37-55 and 74-79 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. In particular, the Examiner alleged that the specification does not disclose a representative number of species of functional groups derived by a chemical reaction with the aldehyde group of a HAS polysaccharide, or a representative number of HAS polysaccharides that can be conjugated to any protein. The Examiner also alleged that the specification does not disclose functional derivatives or fragments of the protein.

To further prosecution, claims 37 and 43-55 have been amended to recite that the HAS and the protein are covalently bonded by a coupling reaction between the terminal aldehyde group of the HAS molecule and a primary amino group of the protein to form a Schiff's base. Applicants' specification adequately describes the presently claimed conjugates. For example, Applicants' specification discloses that "alkyl" in "hydroxyalkylstarch" can include methyl, ethyl, isopropyl, and n-propyl. See, page 5, lines 30-33. In addition, Applicants' specification at page 17, lines 11-32 discloses that the terminal aldehyde group (of the HAS molecule) can be reacted directly with a primary amino group of the protein to form a Schiff's base, which can be reduced to resulting a stable bond between the protein and the HAS. Further, Examples 11-15 at pages 26-28 disclose that the inventors coupled high and low molecular weight HES to albumin,

asparaginase, interleukin-2, and insulin. A person of skill in the art reading these examples would understand that the coupling in each case occurred via a Schiff's base, since in each case a reducing agent (sodium cyanoborohydride ( $\text{NaBH}_3\text{CN}$ ) or sodium borohydride ( $\text{NaBH}_4$ )) was added to the reaction mixture. Thus, Applicants' specification discloses multiple examples of the presently claimed conjugates. Given the above, a person of skill in the art at the time the application was filed would have appreciated that Applicants invented and were in possession of the conjugates recited in present claims 37 and 43-55.

In light of the above, Applicants respectfully request withdrawal of this rejection of claims 37 and 43-55 under 35 U.S.C. § 112, first paragraph.

The Examiner rejected claims 37-55 and 74-79 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Examiner alleged that given the unpredictability based on the different unknown structures of materials, such as the genus of HAS polysaccharides, the functional groups on the HAS polysaccharide, and the functional groups on the protein that are being used to conjugate the polysaccharide with the protein, undue experimentation would be required to make and used the claimed conjugates.

Claims 37 and 43-55 have been amended to recite that the HAS and the protein are covalently bonded by a coupling reaction between the terminal aldehyde group of the HAS molecule and a primary amino group of the protein to form a Schiff's base. The presently amended claims are fully enabled. This is particularly true given that (a) the level of skill in the art is high, as acknowledged by the Examiner; (b) the amended claims specifically recite the functional group of the HAS molecule and the functional group of the protein involved in the formation of the HAS-protein conjugate; and (c) the claims specifically recite that the HAS-protein conjugation proceeds via formation of a Schiff's base in the covalent bonding. The claims are not broadly drawn. Rather, the specific characteristics of the coupling reaction are particularly recited.

Further, Applicants' specification describes how to make the presently claimed conjugates. *See, e.g.*, page 17, lines 11-32, which discloses that the terminal aldehyde group (of the HAS molecule) can be reacted directly with a primary amino group of the protein to form a

Schiff's base, and lists numerous reducing agents that can be used to convert a Schiff's base to an amine bond. The specification also provides numerous working examples of HAS-protein coupling reactions proceeding through the formation of a Schiff's base. Examples 11-15 at pages 26-28 of the specification disclose specific conditions that were employed for coupling low and high molecular weight HES with multiple proteins. The exemplar proteins differ not only in primary and tertiary structure and molecular weight, but also in biological activity. In addition, the specification at page 18, lines 8-30 disclose methods for evaluating the efficiency of the coupling reaction, and the efficiency of the coupling reaction is reported in each of Examples 11-15. Thus, Applicants' specification provides more than adequate guidance for making the presently recited conjugates.

Further, the paragraphs at pages 19 and 20 of Applicants' specification describe downstream applications of the recited conjugates. For example, this section of the specification discloses specific uses of the HAS-protein conjugates for prophylactic and therapeutic pharmaceutical compositions, and discusses suitable methods for administering such compositions. In addition, the specification at pages 19 and 20 provides guidance for using the HAS-protein conjugates for *in vitro* applications. Thus, Applicants' specification provides more than adequate guidance for using the presently recited conjugates.

Given the high level of skill in the art and the detailed guidance provided by Applicants' specification, no undue experimentation would have been required for a person of skill in the art at the time Applicants filed to make and use the presently recited conjugates. In light of the above, Applicants respectfully request withdrawal of this rejection of claims 37 and 43-55 under 35 U.S.C. § 112, first paragraph.

#### Rejections under 35 U.S.C. § 102

The Examiner rejected claims 37, 41, 42, 44, 45, 48-53, 55, 74, 78, and 79 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,083,909 (the '909 patent). The Examiner asserted that the '909 patent describes a hemoglobin-HES conjugate in which the free amino groups of hemoglobin and the oxidized form of HES are linked by selective amide bonds.



The Examiner also rejected claims 37, 41, 42, 44-48, 50-53, 55, 74, and 79 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 4,900,780 (the '780 patent). The Examiner asserted that the '780 patent discloses hemoglobin conjugated to HES via an amide linkage.

In addition, the Examiner rejected claims 37, 38, 41, 42, 50-53, 55, 74, 75, and 79 under 35 U.S.C. § 102(b) as allegedly being anticipated by the Beez *et al.* reference (translated version of German Patent Application 26 16 086). The Examiner stated that the Beez *et al.* reference describes the conjugation of HES with hemoglobin via an amide bond between the terminal aldehyde of the HES and the hemoglobin.

Again, to further prosecution, claims 37 and 43-55 have been amended to recite conjugates in which the HAS and the protein are covalently bonded by a coupling reaction between the terminal aldehyde group of the HAS molecule and a primary amino group of the protein to form a Schiff's base. None of the cited references discloses a conjugate as recited in the present claims. For example, at no point does the '909 patent disclose an amine bond between a protein and a HAS molecule, let alone an amine bond that is the result of reducing a Schiff's base. Likewise, the '780 patent and the Beez *et al.* reference fail to disclose a HAS molecule coupled to a protein via a covalent bonding that is the result of a coupling reaction between the terminal aldehyde group of the HAS molecule and a primary amino group of the protein to form a Schiff's base. Thus, the '909 patent, the '780 patent, and the Beez *et al.* reference fail to anticipate the present claims.

In light of the above, Applicants respectfully request withdrawal of the rejections of claims 37, 44-53, and 55 under 35 U.S.C. § 102.

### CONCLUSION

Applicants submit that claims 37 and 43-55 are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned agent if such would further prosecution.

Please charge \$120 for the Petition for Extension of Time fee, and apply any other charges or credits, to deposit account 06-1050.

Respectfully submitted,

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